Thalamocortical disconnection affects the somatic marker and social cognition: a case report

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Thalamo-cortical disconnection affects the somatic marker and social cognition: a case report

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The authors report no conflict of interest.

Authors' Contribution

LS, MB, MB conceived the study;

LS MB, CO, CDD, LF performed neuropsychological tests

LS, CDD, performed MRI acquisition

LS, CDD, CO analysed data

LS, MB, CO, MB wrote the draft

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Thalamo-cortical connectivity was characterised in a patient with bilateral infarct of the thalami, without evidence of cognitive deficits in everyday life. Patient underwent social and emotional tests, Iowa Gambling Task (IGT), with and without concomitant heart rate variability (HRV) recording and at 3T-MRI to assess thalamo-cortical connectivity. Patient showed impairment at the IGT, in somatic marker, in emotions and theory of mind. MRI documented a bilateral damage of the centromedian-parafascicular complex. Patient's thalamic lesions disconnected brain areas involved in decision-making and autonomic regulation, affecting the somatic marker and resulting in the neuropsychological deficit exhibited by L.C.

Keywords: thalamic lesions, MRI, connectivity, Social cognition, somatic marker.

1. Introduction

The thalamus mediates communications between brain's sensory/motor/associative areas through thalamo-cortical connections (Wiegell, Tuch, Larsson, & Wedeen, 2003). Different thalamic nuclei exhibit reciprocal connections to distinct prefrontal regions, hence playing a role in various cortico-subcortical circuits (Masterman & Cummings, 1997; Liebermann, Ploner, Kraft, Kopp, & Ostendorf, 2013). The thalamus is involved in several cognitive functions by modulating different brain networks (Liebermann, et al., 2013; Carlesimo, Lombardi & Caltagirone, 2011). For instance, anterograde memory deficits have been associated to damage to the anterior thalamic nuclei or to the mammillo-thalamic tract (MTT) (Carlesimo et al., 2011; Van der Werf et al., 2003; Carlesimo et al., 2007). Conversely, executive dysfunctions result from lesions involving the medial-dorsal (MD), the midline or the intralaminar nuclei (Liebermann, et al., 2013; Carlesimo et al., 2011; Van der Werf et al., 2003; Carlesimo et al., 2007). In this picture, investigating the thalamic neurophysiological functions means assessing its role in the context of modulation of networks' connectivity, and clinical cases of focal thalamic lesions offer the opportunity to address these questions *in vivo*. A large amount of information on brain connectivity comes from diffusion tensor imaging (DTI) studies. Thanks to DTI-based tractography (Mukherjee, Chung, Berman, Hess, & Henry, 2008), white matter tracts can be reconstructed, and measures of local microscopic tissue integrity/damage can be obtained (Bozzali, Serra, & Cercignani, 2016; Serra et al., 2012) providing information on the pathophysiological role of disconnection in determining patients' clinical features (Serra et al., 2012; Bozzali et al., 2012; Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008). However, the connectivity patterns of the thalamus are extremely complex and based on very small white matter bundles, thus making their tractographic reconstruction particularly challenging. Beherens and co-workers (2003) developed a DTI-tractography based method that allows to assess patterns of anatomical connectivity between thalamic subfields and cortical brain areas. It is possible to collect DTI data from a cohort of healthy individuals, to assess their average patterns of regional thalamic connectivity to the whole cerebral

cortex to yield an "atlas" of the most likely cortical region each thalamic voxel is connected to. This atlas can be overlapped onto the normalised brain scan of a patient with a thalamic lesion, providing indications of thalamic-cortical connections likely impaired by the lesion. The Oxford thalamic connectivity atlas (Jenkinson, Bannister, Brady, & Smith, 2002; Smith et al., 2004; Woolrich et al., 2009) is provided with the FMRIB software library (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) and includes 7 sub-thalamic regions, connecting to large cortical areas. For the purpose of understanding subtle cognitive/behavioural deficits, a more detailed characterisation of the pattern of connectivity with specific Brodmann areas is required. Therefore, we recently built our own atlas of thalamic connectivity with the prefrontal cortex, and we used it to investigate the pattern of thalamo-cortical connectivity in two patients with a broadly similar distribution of thalamic lesions, but substantial differences in their cognitive presentation (Serra et al., 2013). The different impact of the thalamic lesions on the thalamic-cortical connectivity supports potential pathways involved in cognitive processes.

Here we aimed to characterise the thalamo-cortical connectivity in a single patient (L.C.) with a bilateral infarct of the thalamus, mainly involving the centromedian parafascicular (CM-pf) complex, and mild cognitive and behavioural complaints. The originality of the case lies in the location of L.C.'s lesion, distributed within a nucleus – the CM-pf – previously described as involved in producing apathy and dysexecutive deficits (Serra et al., 2013). Conversely, L.C. did not present such deficits, but instead reported "increase of emotionality and anxiety". In order to clarify the connections between the CM-pf complex and the prefrontal brain areas, we used our previously created thalamo-cortical connectivity atlas, in combination with an extensive assessment of cognitive functions, and of autonomic nervous system regulation. Autonomic functions influence the expression of emotional feeling states, and both the thalamus (Massimini et al., 2000) and the prefrontal cortex (Thayer et al., 2012) have been directly implicated in the variability of the heart period, i.e. heart rate variability (HRV). Tonic HRV refers to HRV taken at one time point (i.e.,

baseline or resting HRV). On the other hand, phasic HRV represents the response to a stimulus and is usually measured as the change in HRV from two different time points (i.e., reactivity). High tonic HRV reflects robust parasympathetic control, via the vagus nerve, on the heart, and has been associated with effective self-regulation as well as with optimal performance on executive tasks (Ottaviani et al., 2018). Phasic HRV, however, may be seen as adaptive or not depending on the situation. Reduced phasic HRV is adaptive when the individual is facing a stressor (e.g., Laborde et al., 2017), whereas it becomes dysfunctional in the absence of an actual stressor, as for example during the anticipation of a potential future threat or during rumination about past negative events (see Ottaviani, 2018 for a recent review).

It is therefore conceivable that L.C.'s thalamic lesions may produce higher-level dysfunction also through an involvement of the autonomic nervous system. To test this hypothesis, we measured HRV both at rest and during a decision-making task. We hypothesized that L.C. would show low levels of tonic HRV as well as an impairment in task related autonomic response (i.e., inappropriate phasic HRV responses to punishments and rewards).

2. Material and Methods

2.1 Case report

The clinical history of L.C. was previously described (Liguori et al., 2015). Briefly, L.C. (38-year-old male, with 13 years of formal education, journalist) suffered from a bilateral thalamic stroke due to ephedrine and naphazoline abuse, which probably caused a prolonged vasospasm of the artery of Percheron (an anatomical variant of the posterior cortical artery) (Liguori et al., 2015). When in 2016 (2 year after the acute event), the patient came to our observation, he did not complain of any specific cognitive deficit or impairment in his everyday life, with the exception of a self-reported "increase of emotionality and anxiety".

Local Ethical Committee of Santa Lucia Foundation approved the project. Written informed consent was obtained from L.C. before study initiation. All procedures performed in this study are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2 MRI acquisition and data analyses

L.C. underwent MRI-3T brain scanning (Siemens, Medical solutions, Erlangen, Germany) including the sequences: (a) dual-echo spin echo (DE-SE) (TR=5000 ms, TE=20/100 ms); (b) fast-fluid attenuated inversion recovery (FLAIR) (TR=8170 ms, TE=96 ms, TI=2100ms); (c) 3D T1-weighted (TR=7.92 ms, TE=2.4 ms, TI=210 ms, flip angle = 15°). For the dual-echo and FLAIR sequences, 52 contiguous interleaved axial slices were acquired with a 2 mm slice thickness, with a 192 x 256 matrix over a 256 mm x 256 mm field of view, covering the whole brain. The T1-weighted image was acquired in a single slab, with a sagittal orientation a 224 x 256 matrix size over a 256 x 256 mm^2 field of view, with an effective slice thickness of a 1mm.

Patient's thalamic lesions were outlined by an experienced rater using the T1-weighted image as a reference. The same guidelines followed for previous studies (Carlesimo et al., 2007; Serra et al., 2013; Carlesimo et al., 2011) were used to create masks of the lesions using FSLview (http://www.fmrib.ox.ac.uk/fsl/). The T1-weighted image was warped to the T1-weighted MNI atlas (available in FSL), using the FMRIB's Nonlinear Image Registration Tool (FNIRT) (Andersson, Jenkinson, & Smith, 2007), and the same transformations were applied to the lesion mask. Finally, the patient's normalised lesion mask was superimposed onto the previously created atlas of thalamo-cortical connections (Serra et al., 2013) to assess the most likely pattern of disconnection induced by each lesion.

2.3 Thalamo-cortical connectivity atlas

Data collection and analysis used to produce the atlas of thalamic connectivity with the prefrontal BAs are previously described in detail (Serra et al., 2013). Briefly, it was obtained using DTI data from 19 healthy subjects [all men; median [range] age=30 [22-40] years], using diffusion-weighted images [twice-refocused SE echo-planar imaging (EPI) sequence (TE/TR=90/8500 ms, b_{max}=1000 smm^{-2}, voxel-size 2.3 x 2.3 x 2.3 mm^3) with diffusion gradients applied in 81 non-collinear directions (Cercignani, Embleton, Parker & Bozzali, 2012). The whole thalamus was defined as the "seed-region", while the functionally-labelled prefrontal cortices supplementary motor cortex (SMA, BA6), frontal eye fields (BA8), dorsolateral prefrontal cortex (DLPFC, BA9), anterior prefrontal cortex (BA10), anterior cingulate cortex (ACC, BA32), Broca's area (BA44), dorsolateral prefrontal cortex (DLPC, BA46) were set as "target". These specific BAs were chosen as they are implicated in cognitive and behavioural functions (Serra et al., 2013). Then, probabilistic tractography (Parker, Haroon, & Wheeler-Kingshot, 2003) implemented in CAMINO was used to assign to each voxel in the seed some probability of being connected to each of the targets. The seed voxels were thus classified as connecting to the target with maximum probability, and each cluster of voxels connecting to the same target is labelled as belonging to the same substructure. As we were interested in the connections between the thalamus and the prefrontal cortex only, voxels that showed a probability of connection lower than 0.5 to any of the prefrontal regions were discarded, as these voxels are more likely to be connected to other regions of the cortex.

2.4 Psychopathological assessment

L.C. underwent a psychological assessment including the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (Radloff, 1977) to assess depressive symptoms; the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) to assess state (STAI-S) and trait (STAI-T) anxiety; the Barratt Impulsiveness Scale-11 (BIS-11) (Reise, Moore, Sabb, Brown, & London, 2013) to assess

impulsivity (Fossati, Di Ceglie, Acquarini, & Barratt, 2001); and the Empathy Quotient (Baron-Cohen & Wheelwright, 2004; Preti et al., 2011) to measure the cognitive and affective aspects of empathy.

2.5 Neuropsychological assessment

L.C. underwent a neuropsychological assessment including:

1) Screening cognitive tests: Verbal and visuo-spatial episodic long-term memory: 15-Rey'sWord List (Immediate and 15-min Delayed recall and Recognition) (Carlesimo, Caltagirone & Gainotti, 1996); Short Story Test (Carlesimo, et al., 2002); Complex Rey's Figure (Immediate and 20-min Delayed recall) (Carlesimo, et al., 2002); short-term memory: Digit span and the Corsi Block Tapping task (Monaco, Costa, Caltagirone, & Carlesimo, 2013); executive functions: Phonological Word Fluency (Carlesimo et al., 1996); Modified Card Sorting Test (MCST) (Nocentini, Di Vincenzo, Panella, Pasqualetti, & Caltagirone, 2002); and Trail Making Test (Giovagnoli et al., 1996); Reasoning: Raven's Coloured Progressive Matrices (Carlesimo et al., 1996).

2) Iowa Gambling Task (IGT) (Bechara & Damasio, 2002): to assess risk preferences by simulating real-life decision-making using uncertain rewards and penalties. L.C. was presented with 100-cards from 4 virtual decks (A, B, C, D) of cards on a computer screen, and he was instructed that every time he chose a card he would have won or lost some game money. The goal of the game is to win as much money as possible. Decks A and B are disadvantageous (leading to an overall loss), while decks C and D are advantageous (leading to an overall gain). L.C. could not predict when a penalty will have occurred, nor calculate with precision the net gain or loss from each deck. He also did not know how many cards had to be turned before the end of the game. Finally, the overall total net-score was calculated [(C+D)-(A+B)].

L.C. was administered twice the IGT at 2 weeks interval. In the second occasion, a simultaneous monitoring of his HRV was performed (see below).

3) Social Cognition Battery (Prior, Marchi, & Sartori, 2003): a comprehensive tool to evaluate different aspects of social cognition, including the Theory of Mind, the emotional attribution, the social abilities situation, the moral and conventional knowledge.
4) PENN Emotion Recognition test (Kohler et al., 2003): a test with 40 neutral, sad, happy, angry and fearful facial expressions that must be recognised.

For all employed tests, data for score adjustment (based on sex, age and education) were derived from Italian normative when available (see corresponding references). For each test, normality cut-off scores were determined as the adjusted score in the normative sample that corresponded to the lower limit of the 95% tolerance interval for a confidence level of 95%.

2.6 Psychophysiological assessment

HRV was recorded as beat-to-beat intervals in ms with the Bodyguard 2 (Firstbeat) HR monitor (Parak et al., 2015). Recording started at the beginning of the IGT and the recording duration was about 30 min. HRV was assessed by computing the root mean square of successive beat-to-beat interval differences (RMSSD), which reflects vagal regulation of HR (Camm et al., 1996). Outlier and artefact detection as well as HRV analyses were performed using Kubios HRV software (Tarvainen, Niskanen, Lipponen, Rantas-Aho, & Karjalainen, 2014). We obtained HRV data for two intervals of interest: (1) 5s intervals after each card was turned (reward/punishment HRV); and (2) intervals between the end of each 5s reward or punishment interval and before the next card selection (anticipatory HRV). We then obtained an average of reward/punishment HRV and an average of anticipatory HRV. Although the Somatic Marker Hypothesis (Damasio, Tranel, & Damasio, 1991) has been more often tested by the use of skin conductance, this is not the first study that used HRV during performance on the IGT (Damasio, 1994).

3 Results

3.1 MRI

A visual inspection of patient's T1-weighted image revealed a bilateral and asymmetrical (right > left) thalamic lesion involving the CM-pf complex (Figure 1). No additional brain abnormality was detectable on the patient's T2-weighted and FLAIR scans.

When overlapping L.C.'s lesions to the connectivity atlas, they fell within thalamic areas which are extensively connected to the prefrontal cortex (Figure 2). In particular, in L.C. lesions voxels were located in the area of parafascicular and reuniens thalamic nuclei projecting to the anterior cingulate cortex (ACC, BA32), and in the area of Centro-median nuclei projecting to the supplementary motor area (SMA, BA6) and to the dorsolateral prefrontal cortex (DLPFC, BA9).

3.2 Psychopathological assessment

L.C. neither presented levels of pathological anxiety (scores of 24 and 25 for STAI-T and STAI-S respectively; cut-off $\geq$ 30) nor symptoms of depression (score on the CES-D = 14; cut-off $\geq$ 16). However, L.C. reported a total score of 46 on the BIS-11 (Cognitive/Attentional Impulsiveness score = 12; Motor Impulsiveness score = 13; Non-Planning Impulsiveness score = 21). BIS-11 total scores between 52 and 71 should be thought of as within normal limits for impulsiveness, whereas scores lower than 52 are usually representative of an individual who is extremely over-controlled, and a score of 72 or greater indicates a high level of impulsiveness (Knyazev & Slobodskaya, 2006).

3.3 Neuropsychological assessment

As shown in Table 1, L.C. reported scores above the Italian cut-off of normality in each neuropsychological test of the screening battery, with the only exception for the of Rey's Complex Figure (copy, c-CRFT, and immediate and delayed recall).

Table 2 reports L.C.'s social, emotional and decision-making performances. L.C. showed impaired performances at the IGT at both assessments (net-scores = -4 and -8, respectively). No evidence of

improvement due to test-rest effect was detected. As shown in Figure 3, simultaneous HRV assessment revealed that L.C. showed HRV decreases after the choice of the disadvantageous (A+B, in red) decks, and HRV increases after the choice of the advantageous (C+D, in green) decks, suggestive of an adaptive response to punishment and rewards. However, in the anticipatory phase, L.C. showed a dysfunctional pattern characterised by higher HRV before the choice of the disadvantageous decks, and lower HRV before the choice of the advantageous decks, a pattern that indicates the lack of emotion-based learning in this patient. Typically, the response to reward and punishment is learned, and such somatic state information (i.e., somatic marker) guides subsequent choices, making non-pathological individuals more likely to approach advantageous decks and to withdraw from disadvantageous decks (Damasio et al., 1991; Damasio, 1994).

It should be noted that L.C. also presented with baseline HRV values of 13.4 ms^2, which are below the normative values for his age and body mass index (42 $\pm$15 ms^2) (Ninan, Sandercock & Brodie, 2010), indicating low resting vagally-mediated HRV.

Finally, L.C. reported pathological scores at some sub-tests of the Social Cognition battery, specifically at Theory of Mind, emotional attribution (Fear and Angry), and Social situation subtests (in the recognition of Normative behaviour). L.C. reported also poor performances (below the 50% of accuracy) at the PENN Emotion Recognition Test (Fear and Angry). Taken together these deficits made the patient less responsive to the emotional feelings of the other people, less able to understand what the people thought or felt. In everyday life, L.C. showed an intransigent and rigid behaviour scarcely adaptable to the social environment. As a consequence, the patient showed a socially isolated behaviour with poor interpersonal relationship characterised by superficial interactions.

4. Discussion

This study extends the knowledge we currently have about both the thalamo-cortical connectivity, and the role played by the thalamus in higher-level cognitive functions. We had previously defined a connectivity atlas using connectivity-based segmentation to delineate the probability of structural connectivity between each voxel of the thalamus and the areas of the prefrontal cortex mainly involved in executive functions (SMA, BA6; frontal eye fields, BA8; DLPFC, BA9 and BA46; anterior prefrontal cortex, BA10; ACC, BA32; Broca's area, BA44) in a group of healthy subjects (Serra et al., 2013). Here, following the same procedure, we overlaid the thalamic lesions of a patient (L.C.) suffering from bilateral thalamic lesions and minimal daily cognitive complaints, to the connectivity atlas, to assess the connections most likely affected by the lesions. The connectivity-based segmentation approach revealed that L.C.'s lesions fell in the parafascicular/reuniens thalamic nuclei projecting to the ACC (BA32) and in the area of centro-median nuclei projecting to the SMA (BA6) and to the DLPFC (BA9). L.C. suffered from mild behavioural dysexecutive syndrome, characterised by visuo-spatial planning deficits, decision-making, and social cognition disorders, with a sparing of attention, set-shifting abilities, and no evidence of apathy but increased emotionality and anxiety. He also reported a minimal impact of this condition on his daily life functioning. L.C. obtained scores on the BIS-11 below the normative range suggesting a hyper-controlled personality with difficulties in focusing and with troubles in making quick decisions.

From a neuropsychological viewpoint, L.C. showed pathological performances on the c-CRFT (and at immediate and delayed recall as a consequence), a test assessing both the more basic (such as the grapho-motor ability) and the higher aspects of the constructional praxis (such as the visuo-spatial planning abilities) (Serra et al., 2014; Grossi Conson & Trojano, 2006). A qualitative analysis of the c-CRFT revealed the presence of a selective visuo-spatial planning deficit (resulting in a not appropriate sequencing of different figure segments and in the simplification of the figure) in the absence of grapho-motor deficits. This planning deficit led to the lack of the global strategy,

resulting in a juxtaposition of the single elements of the figure. A recent study (Cona & Semenza, 2017) showed that the sequence processing depends on the integrity of the SMA (BA6), which contributes to the integration of sequential elements into higher-order representations, regardless of the nature of such elements. We can therefore hypothesise that the altered connectivity observed between CM-pf complex and the BA6 may account for the visuo-spatial planning deficits shown by L.C.

Moreover, L.C. showed pervasive decision-making impairment as measured by the IGT. The IGT was administered twice, 15 days apart, and no evidence of improvement due to a learning effect was detected. In our opinion, the low net-score obtained during performances on the IGT does not reflect the patient's inclination toward risk-taking because this would be in contrast with his extremely low impulsivity as measured by the BIS. When we looked at the autonomic responses following the selection of each card, we found that L.C. failed to use to so-called somatic marker (Damasio et al., 1991; Damasio, 1994) to either encourage or discourage his choices. The Somatic Marker Hypothesis (Damasio et al., 1991; Damasio, 1994) posits that each behavioural choice is associated with unconscious somatic responses evoked by its previously learnt consequences and such somatic marker covertly guides human decision-making (Damasio et al., 1991; Damasio, 1994). Somatic marker impairment has been previously found in patients with prefrontal lesions (Bechara, Damasio, Damasio, & Anderson, 1994), mainly in those with damage in the more ventromedial part of the ACC (BA32). We hypothesised that the somatic marker deficit that we observed in L.C. could be due to the disconnection between the CM-pf complex and ACC (BA32). A recent study documented pathological performances on the IGT and a somatic marker deficit in a patient with microstructural damage of the thalamic radiations, hypothesising that a reduced afferent feedback to the brain can produce a less efficient decision-making (Yasuno et al., 2014). Moreover, Vogt (2014) highlighted that ACC (BA32) is a functionally complex brain area, which conveys different information including those regarding emotional regulation (in particular fear),

emotional awareness, reward, and decision-mediated feedback, as well as autonomic regulation. Consistently, L.C. had low baseline HRV, indicating autonomic nervous system dysregulation. Resting low HRV has been associated with difficulties in emotion regulation, recognition, and expression (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012; Williams et al., 2015; Tuck, Grant, Sollewrs, Booth, & Consedine, 2016), in line with the impaired performance of the patient on the Theory of Mind and emotion recognition tests. In fact, L.C. showed difficulties in the processing of specific emotions, particularly fear and anger (both in the attribution and in the recognition tests). In our view, patient's lesions within the CM-pf complex affected both autonomic regulation and emotional processing by disconnection mechanisms with the ACC (BA32).

L.C. also obtained pathological scores both at the Theory of Mind-story test and at tests assessing the emotional attribution and emotional recognition. We suppose that the patient's thalamic lesions can also account for these deficits. Several studies (Mar, 2011; Serra et al., 2016) reported that ACC (BA32) and DLPFC (BA9) are involved in theory of mind ability. Therefore, we postulate that the damage of the CM-pf complex can explain patient's deficit by a disconnection mechanism. In this view, patient's social cognition deficits interfered with his ability to mentalize the thoughts, the feelings and the emotional needs of other people. As a consequence, the patient was not able to react appropriately in the social context (Adolphs, 2001; Amodio and Frith, 2006; Beer et al., 2006), due to inability to recognize correctly the social signals. Therefore, the patient showed a poor flexible and adaptive response to the environmental requests. Although L.C. recognized the inappropriateness of his social reactions, he was not fully awareness of the real impact of his social cognition difficulties in daily life. However, he generally perceived himself as being poorly goal-oriented and therefore he experimented increasing levels of anxiety.

In our perspective, L.C. did not reveal a major frontal disorder affecting extensively his daily life, because he had focal thalamic lesions limited to the CM-pf complex. In our previous study (Serra et al., 2013), we described a patient with a more severe dysexecutive syndrome, (characterised by

planning deficits, severe apathy, inertia, and affective flattening) related to the damages involving both the CM-pf complex and the MD nucleus, bilaterally. In our opinion, the damage of the MD is necessary to produce severe behavioural and cognitive symptoms, affecting daily life functioning. Conversely, a selective damage of the CM-pf complex of the thalamus produces slighter emotional, affective and cognitive disabilities, which result more in a kind of social inappropriateness than in a general cognitive incompetence. Indeed, we retain that the disconnection in the thalamo-cortical circuitry causes a partial de-afferentation, leading at less severe cognitive impairment than those observed for cortical damages. It is important to highlight that the thalamic parcellation used for this patient was based on tractography data from an independent group of healthy subjects. Given inter-individual anatomical variability, and the well-known limitations of tractography (Schilling et al., 2019), results obtained at single-subject level must be evaluated with caution. Nevertheless, the neuropsychological and autonomic data fit well with the connectivity pattern identified in this case, thus reinforcing our conclusions.

To conclude, this study extends the knowledge about the contribution of the different nuclei of the thalamus in cognitive and behavioural functioning and supports the role of the thalamus in the regulation of the autonomic nervous system. Additionally, this study proposes a procedure that might be used, at single subject level, in clinical setting to clarify the impact of focal thalamic lesions on higher-level dysfunctions.

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Table 1. Performance scores, adjusted for age, education and gender according to normative data, obtained by L.C. on neuropsychological screening assessment

Neuropsychological tests	Patient L.C.
Verbal long-term memory	
15-Word List:	
Immediate recall (cut-off ≥ 28.5)	38.5
Delayed recall (cut-off ≥ 4.6)	8.9
Recognition cut-off ≥0.92)	1
Short Story:	
Immediate recall (cut-off ≥ 3.1)	3.3
Delayed recall (cut-off ≥ 2.8)	2.5
Visuo-spatial long-term memory	
Rey's Complex Figure	
Immediate recall (cut-off ≥ 6.4)	**1.92**
Delayed recall (cut-off ≥ 6.3)	**0.0**
Verbal short-term memory	
Digit Span forward (cut-off ≥ 3.7)	5.61
Visuo-spatial short-term memory	
Corsi Span forward (cut-off ≥ 3.4)	5.6
Executive functions	
Phonological verbal fluency (cut-off ≥ 17.3)	29.4
Modified Card Sorting Test Criteria achieved (cut-off ≥ 5.04)	6.0
Digit Span backward (cut-off ≥ 2.6)	3.6
Corsi Span backward (cut-off ≥ 3.0)	4.6
Trail making test	
Part A (cut-off ≤ 94)	34.1
Part B (cut-off ≤ 283)	85.4
Part B-A (cut-off ≤ 187)	51.3
Reasoning	
Raven's Progressive Matrices (cut-off ≥ 18.9)	22.8
Constructional praxis	
Rey's Complex Figure-Copy (cut-off ≥23.7**)**	**15.3**

Pathological performances are reported in bold

Table 2. Performances obtained by L.C. on neuropsychological experimental assessment

Neuropsychological tests	**Patient L.C.**
Decision making:	
Iowa Gambling Task before HRV registration (C+D>A+B)	
A+B	**52**
C+D	**48**
(C+D)-(A+B)	**-4**
Iowa Gambling Task during HRV registration (C+D>A+B)	
A+B	**54**
C+D	**46**
(C+D)-(A+B)	**-8**
Social cognition battery	
Theory of Mind-stories (cut-off ≥12)	**9**
Emotional attribution:	
Sad (cut-off ≥6)	6
Fear (cut-off ≥8)	**4**
Embarrassment (cut-off ≥8)	11
Disgust (cut-off ≥2)	3
Happy (cut-off ≥10)	8
Angry (cut-off ≥6)	**4**
Envy (cut-off ≥1)	1
Social Situation Test:	
Normative behaviour (cut-off ≥13)	**12**
Violation of conduct (cut-off ≥22)	23
Severity of violation (cut-off ≥45)	61
Moral and conventional knowledge:	
Not permitted moral behaviours (cut-off ≥6)	6
Severity not permitted moral behaviours (cut-off ≥39)	60
Not permitted moral behaviours without rules (cut-off ≥11)	12
Not permitted conventional behaviours (cut-off ≥5)	6
Severity of not permitted conventional behaviours (cut-off ≥20)	57
Not permitted conventional behaviours without rules (cut-off ≥6)	12
PENN Emotion Recognition test (Male faces % of accuracy):	
Angry	**25%**
Sad	62.5%
Fear	**37.5%**
Disgust	75%
Happy	100%
Neutral	50%
PENN Emotion Recognition test (Female faces % of accuracy):	
Angry	62.5%
Sad	87.5%
Fear	75.0%
Disgust	75.0%
Happy	100%
Neutral	62.5%
Empathy quotient (cut-off ≥30)	66

Pathological performances are reported in bold.

Figure legends.

Fig 1. Macroscopic thalamic damage in patient L.C.

Panel A show the bilateral thalamic damage detectable on T1-weighted images of the patient L.C, revealing an asymmetrical involvement of the thalamus, with the right lesion considerably larger (from y=-22 to y=-15 in MNI coordinates) than the left one (from y=-22 to y=-20 in MNI coordinates). Panel B shows a magnification of the patient's lesion showing the involvement of the Centro median parafascicular complex (CM-pf complex). Panel C illustrates on a modified version from the second edition of the "Atlas of the Human Brain" (Mai, Assheuer & Paxinos pp. 149–167; 2004) the involved Centro median nucleus (in green), and the parafascicular nucleus (in red) forming the CM-pf complex. See text for further details.

Abbreviations CM-pf complex= Centro median parafascicular complex; L= left.

Fig 2. Patterns of connectivity between lesions' voxels and prefrontal Brodmann areas.

Patterns of connectivity between lesions' voxels and the Brodmann areas of interest. Lesions are shown in white and overlaid onto the results of thalamic segmentation, using the FSL T1-weighted template in standard space. L.C.'s lesions fell within thalamic areas extensively connected with BAs of the prefrontal cortex (BA32; BA9 and BA6). The patterns of connectivity between lesion voxels and cortical areas are consistent with the knowledge we have of thalamic nuclei projections.

For the purpose of the illustration, there are only reported the most relevant BAs in the prefrontal cortex. See text for further details.

Abbreviations: BA=Brodmann area; R=right;L=left.

Fig 3. Heart Rate Variability responses of patients L.C. during the Iowa Gambling Task.

The figure shows the Heart Rate Variability (HRV) response (expressed in milliseconds) during the Iowa Gambling Task's (IGT's). Patient L.C. shows a normal cardiac response during the Punishment and Reward phase characterised by a decrease of HRV during the choice of the disadvantageous (A + B, in red) decks, and an increase of HRV during the choice of the advantageous (C + D, in green) decks. Conversely, in the following Anticipatory phase patient L.C. shows an abnormal response, characterised by higher HRV during the choice of the disadvantageous decks, and a lower HRV during the choice of the advantageous decks. See text for further details.

Abbreviations: HRV= Heart Rate Variability; IGT= Iowa Gambling Task.

Figures

Figure 1

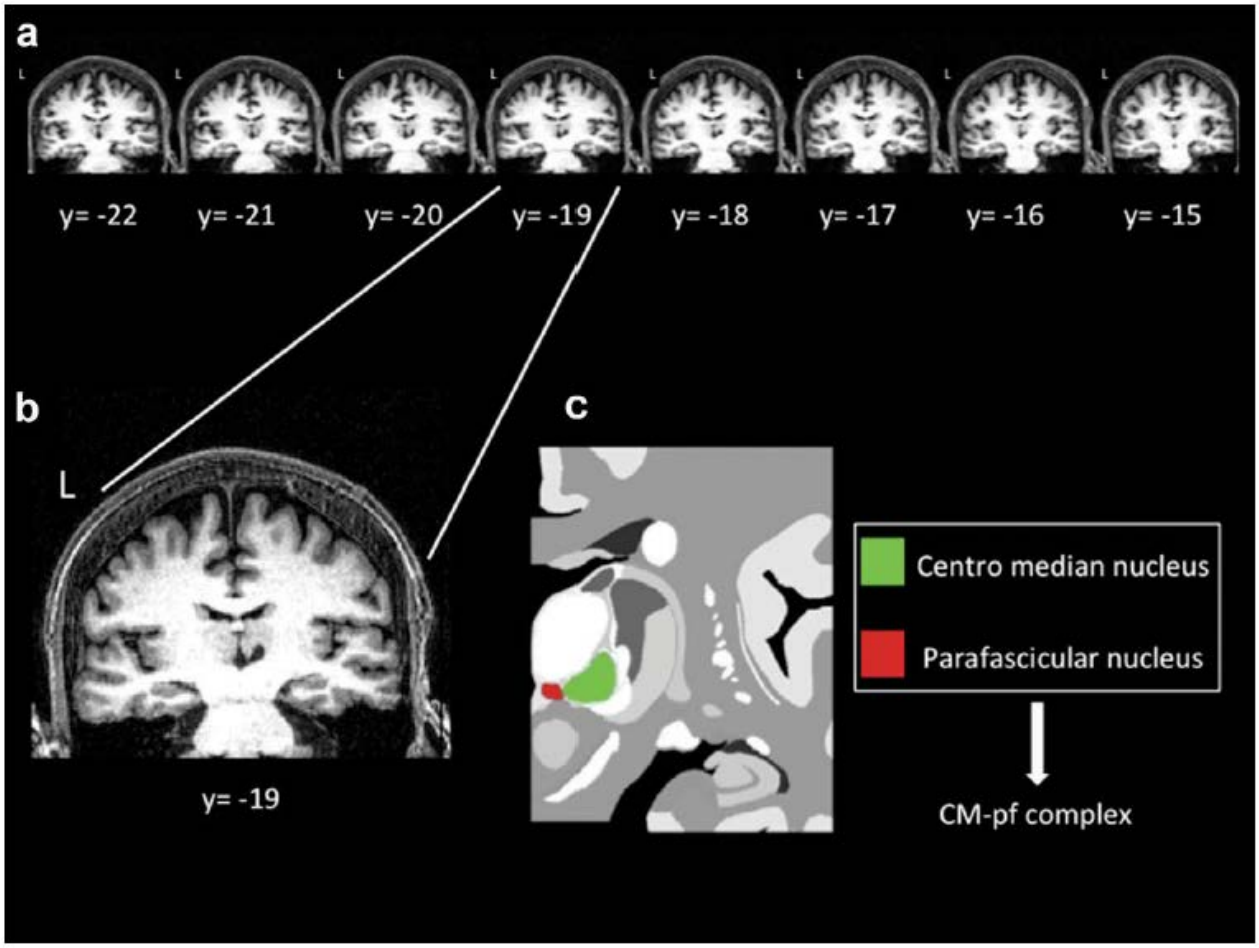


Figure 2

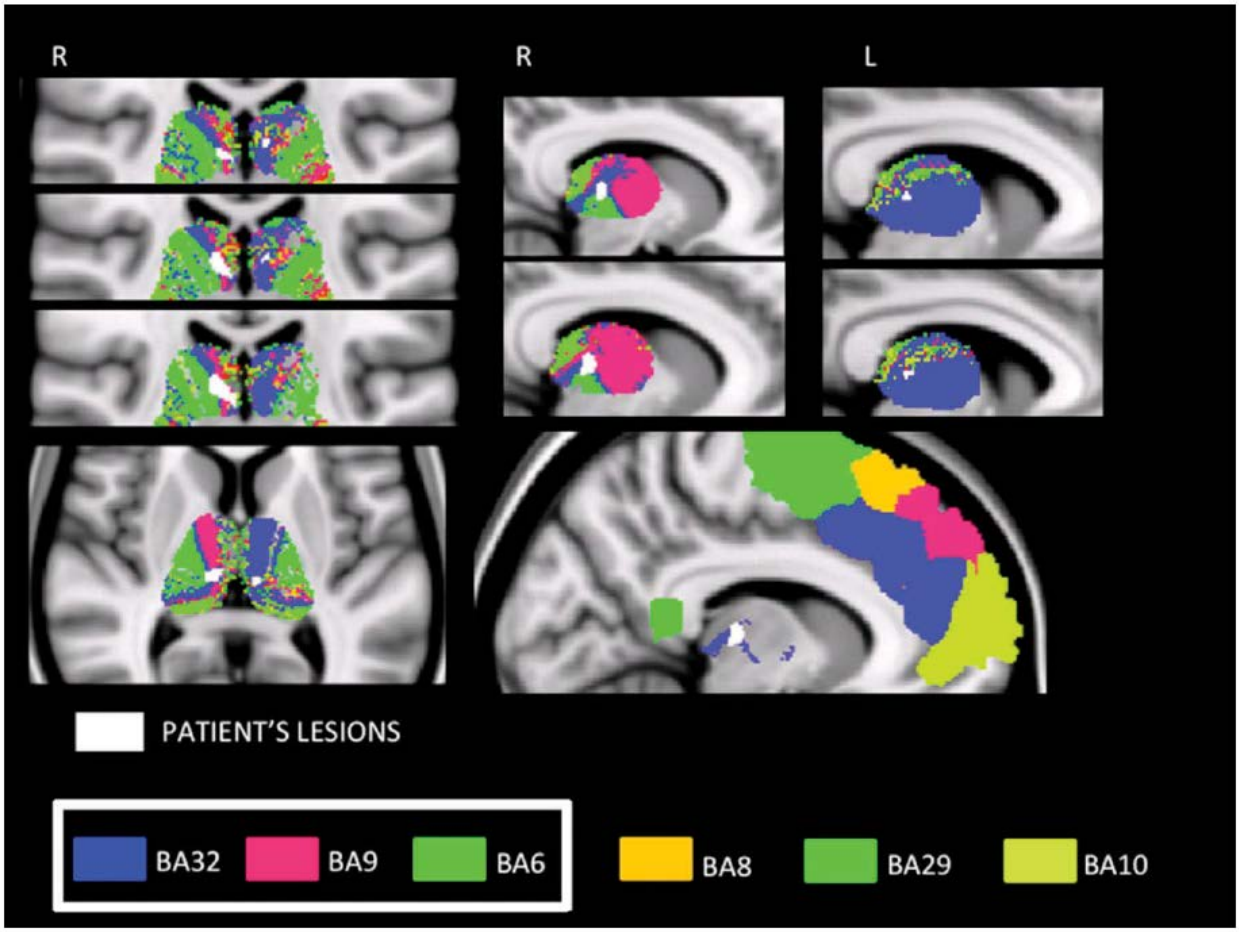
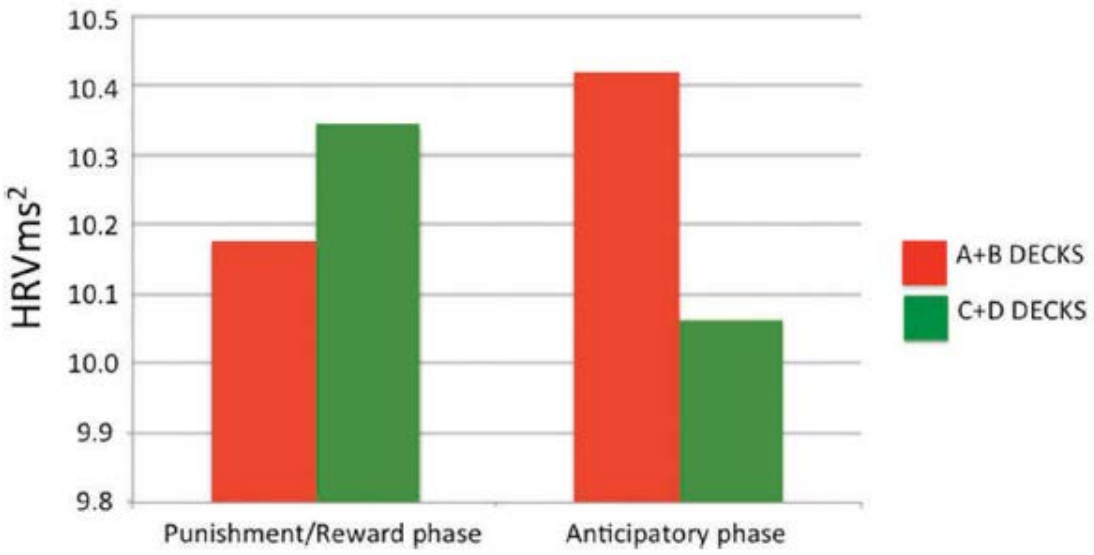


Figure 3


10.5
10.4
10.3
10.2
10.1
10.0
9.9
9.8
HRVms²
Punishment/Reward phase
Anticipatory phase
A+B DECKS
C+D DECKS